Remarks

Claims 1, 3-6, 8-10, 12-14, 16-17 and 19-28 are pending in this application; all of the pending claims have been rejected.

Claim 1 has been amended to correct a typographical error. Claims 20 and 21 have been amended to correct editorial errors. No new matter is added herein. Applicants respectfully request reconsideration of the application based on the following remarks.

REJECTIONS UNDER 35 U.S.C. § 103(A)

Claims 1, 3-6, 8-10, 12-14, 16-17 and 19-28 remain rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Nakatani et al., Vincenti et al., Hayosh and Swanborg, Paty et al., and Jacobs et al. For the reasons discussed below, Applicants respectfully disagree with this rejection.

I. The Cited References

Nakatani

Nakatani et al. disclose a humanized monoclonal antibody B-B10, which binds the interleukin-2 receptor and includes specified complementarity determining regions (see SEQ ID NOs: 1-6). Nakatani et al. disclose that this antibody is of use to treat any tumors, T-cell dependent allergy or autoimmune diseases. As examples of T cell-dependent allergy and autoimmune disease, Natakatani et al. list "myocarditis, diabetes mellitus, myasthenia gravis, lupus erythematosus, Crohn disease, multiple sclerosis, AIDS, Meningitis, Arthritis." Nakatani et al. do not disclose the combination of humanized B-B10 with any other cytokines, let alone with interferon-beta.

Vincenti

Vincenti et al. disclose the use of daclizumab to prevent acute rejection of renal transplantation. Specifically, Vincenti et al. teach that treatment of patients with daclizumab prior to transplantation, and once every other week (along with cyclosporine, azathioprine and prednisone) after transplantation, for a total of five doses, reduced the rate of acute rejection in kidney transplant recipients. However, administration of daclizumab did not result in a significant effect on kidney graft survival at twelve months. Vincenti et al. do not disclose the use of any cytokines, let alone the use of interferon-beta.

Hayosh and Swanborg

Hayosh and Swanborg disclose that a monoclonal antibody to rat IL-2 receptor, OX39 inhibits the activation of effector cells in experimental allergic encephalomyelitis (EAE). Hayosh and Swanborg disclose that OX39 is an anti-Tac antibody. However, Hayosh and Swanborg disclose that OX39 only inhibited EAE effector cell activation when added to cultures at time zero or 24 hours, but did not have any effect on cell activation at 48 hours. Hayosh and Swanborg state that "it will be important to ascertain whether OX39 can suppress EAE inimmunized rats" (see page 3775). Thus, at best, Hayosh and Swanborg make it obvious to try to test anti-Tac antibodies in a rat model of multiple sclerosis. However, Hayosh and Swanborg do not suggest any specific antibodies that could be experimentally tested. Moreover, Hayosh and Swanborg do not disclose the administration of OX39, or any other antibody that binds the IL-2 receptor with other cytokines, let alone interferon-1β.

Paty and Jacobs

Paty et al. describes the administration of interferon-1β-1b to patients with multiple sclerosis. Paty et al. do not suggest, or render obvious, the use of any additional agents with interferon-1β-b for the treatment of multiple sclerosis, let alone the use of a monoclonal antibody such as daclizumab.

Jacobs et al. teaches the administration of interferon-1 beta-1a to patients with multiple sclerosis. Jacobs et al. do not suggest, nor render obvious the use of any additional agents with interferon-1β-1a for the treatment of multiple sclerosis, let alone the use of a monoclonal antibody such as daclizumab.

The prior art does not support a prima facie case of obviousness, as discussed below. Moreover, as the combination of daclizumab with interferon-1β provides an unexpectedly superior therapeutic effect in some subjects who do no respond to daclizumab alone, the claimed methods are not obvious over the cited prior art.

II. The References Cited By The Examiner Are Not Properly Combinable

A predicate of the obviousness rejection is that because the use of anti-interleukin 2 receptor antibodies and interferon beta was known for the treatment of multiple sclerosis, then any effect achieved with the combination of the two agents necessarily would be expected.

This argument presumes that the use of anti-interleukin 2 receptor antibodies had been established as a treatment for multiple sclerosis. The two primary references that the Examiner applies for the purpose of establishing this point are Vincenti and Hayosh and Swanborg. However, these references are at best speculative and, as explained below, demonstrate that if anything the use of anti-interleukin 2 receptor antibodies for the treatment of multiple sclerosis was unpredictable as of the filing date of the present application.

Vincenti

The Office action relies upon Vincenti et al., suggesting that since daclizumab is effective in treating transplant rejection, one of skill in the art would predict that it would be effective for the treatment of multiple sclerosis. However, this is simply not supported by scientific evidence. Van Assche et al. (Gut Online First, April 7, 2006, copy submitted herewith as Exhibit A) studied the efficacy of daclizumab (1 mg/kg and 2 mg/kg) in the treatment of ulcerative colitis, another autoimmune disorder mediated by T cells. Assche et al. conclude that "the results of this placebo-controlled trial show no evidence of a clinical benefit of daclizumab at two direct dose levels to treat active moderate ulcerative colitis....both the high and the low dose of daclizumab failed to demonstrate an increased remission or clinical response rate in the subgroup of patients with active disease." (page 11). Thus, daclizumab was completely ineffective for the treatment of an autoimmune disorder mediated by T cells, namely ulcerative colitis. Assche et al. provide evidence that the results obtained by Vincenti et al. cannot simply be extrapolated to any other condition; even another condition mediated by T cells. Thus, one of skill in the art could not predict the efficacy of daclizumab for the treatment of any other T cells mediated disorder, let alone an autoimmune disorder, based on the teachings of Vincenti et al.

Hayosh and Swanborg

The Office action also relies on the teachings of Hayosh and Swanborg, as documenting that antibodies that bind IL-2 could be effective for the treatment of MS. However, the results obtained by Hayosh and Swanborg are obtained in the EAE model of MS. The EAE model system is not an art-accepted model of MS; results obtained in this system are often questioned by one of skill in the art. Specifically, it is known in the art that many treatments, although successful in pre-clinical EAE trials, were either less effective in patients, worsened disease or cause unexpected adverse effects. Submitted herewith is a copy of Friese et al., Brain 129: 1940-1952, 2006 (Exhibit B), which states (page 1947,

fist column):

> As shown in Table 2, there have been significant problems in multiple sclerosis with virtually all of the agents that appeared beneficial in EAE. Even when efficacy has been replicated in the human disease, additional unexpected adverse effects appeared. These hare precluded successful clinical application in nearly every case.....Worse still, however, many of the EAE results have been actively misleading. Therefore it is difficult to claim any predictive value from positive pre-clinical findings in 'conventional' EAE models....

Another reference, Polman and Uitehaag, 2003, The Lancet Neurology 2:563-566 ("Polman") (Exhibit C), which reviews multiple sclerosis therapies in the clinic as of September 2003, states:

> Although the drugs reviewed here are in different stages of clinical development, they are all intriguing treatment options, particularly because promising results have been obtain from studies in human beings ... rather than in **animal models**, which **are commonly not very predictive of therapeutic efficacy in MS**.

Polman at p. 565, right column, first paragraph under "Conclusions" (**emphasis added**).

Clearly, one of skill in the art would be skeptical of any results obtained in the EAE model described by Hayosh and Swanborg, and would not conclude that the results achieved in this model system could be relied upon to predict any outcome in humans, let alone the outcome with an entirely different agent.

Conclusion

Applicants submit that it is improper to treat the prior art suggested use of anti-interleukin 2 receptor antibodies for the treatment of multiple sclerosis as evidence as an established treatment modality for multiple sclerosis that would be *prima facie* obvious in combination with another established treatment modality for multiple sclerosis, such as interferon beta. As of the filing date of the above-identified application, there were two established therapies for multiple sclerosis: interferon beta and glatiramer acetate (see Polman at page 563, left column). Polman also discusses a "new" treatment as of September 2003 (a year after the priority date for the instant application) and four other emerging treatments with "promising" human clinical data. On the other hand, there were hundreds of unproven treatment modalities for multiple sclerosis (for example, a search of the USPTO's patent publication database for the terms "multiple sclerosis" and "treating" in the claims retrieved almost

4,000 hits).

Thus, while interferon beta was a proven treatment modality for multiple sclerosis at the time of filing the instant application, the use of anti-interleukin 2 receptor antibodies was still unproven and unpredictable. How could a first therapeutic modality (*i.e.*, anti-interleukin 2 receptor antibodies) be obvious with to combine with a second therapeutic modality (*i.e.*, interferon beta), when the utility for the first therapeutic modality was still unproven and unpredictable for multiple sclerosis? The Supreme Court stated in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007):

> Although common sense directs one to look with care at a patent application that claims as innovation the **combination of two known devices according to their established functions**, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR, 127 S.Ct. at 1741 (**Emphasis added**). Thus, a combination of two known treatment modalities may be proper when their functions are **established**, but this is hardly the case for the claimed combination with respect to the anti-interleukin 2 receptor antibody modality.

The Examiner has not articulated why, of all the possible combinations with interferon beta, including the more established therapies described in Polman, one of skill in the art would select an anti-interleukin 2 receptor antibody whose utility for the treatment of multiple sclerosis was unproven and unpredictable. The Examiner's finding obvious the claimed combination can thus only be based on impermissible hindsight, against which the courts have repeatedly cautioned.

III. Even If The References Were Combinable, There Would Have Been No Expectation of Success

To support an obviousness rejection, even if the impermissible combination were made, one of skill in the art must reasonably expect the claimed combination to work (see In re O'Farrell, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed Cir. 1988)). M.P.E.P. § 2143 documents that in order to support a *prima facie* case of obviousness, it must be documented that the claimed methods would be predictable to one of skill in the art based on the prior art. In the present case, the cited prior art simply

does not provide any evidence of the predictability of the claimed methods.

As explained above, the use of anti-interleukin 2 receptor antibodies for the treatment of multiple sclerosis was unproven and unpredictable. However, even assuming, arguendo, that the effectiveness of anti-interleukin 2 receptor antibodies for the treatment of multiple sclerosis had been demonstrated by the prior art such that this function were established, Applicants submit that this would still not be reasonably predictive that the combination of an anti-interleukin 2 receptor antibody and interferon-beta would have efficacy in the treatment of multiple sclerosis. In particular, for the reasons discussed below, the combination of two agents known for the treatment of multiple sclerosis would not be reasonably expected to yield predictable and beneficial results.

In the prior response, Applicants submitted Bowman et al. as evidence that combining agents useful for the treatment of renal failure resulted in adverse effects, such as a higher incidence of acute rejection episodes. The Office action disregards the evidence provided by Bowman et al., because it is directed to the failure of combinations of agent to treat renal failure, and not an autoimmune disease such as multiple sclerosis. Applicants submit that the teachings of Bowman et al. are relevant, since it evidences that combinations of agents may not be effective for the treatment of a disease. However, the following additional evidence is provided in further support of the unpredictability of combining agents for the treatment of immune diseases such as multiple sclerosis.

Submitted herewith is Lee et al., Blood 104: 1559-1564 (Exhibit D), which describes a multi-center, double blinded randomized study of corticosteriods, such as methyprednisolone, with or without daclizumab for the treatment of graft versus host disease (GVHD). The standard of care for the treatment of GVHD is moderate dose corticosteroids, which are immunosuppressive agents. Lee et al. disclose that daclizumab was shown to be efficacious for the treatment of steroid refractory GVHD (see the introduction, citing to Przepiorka et al., Blood 95: 83-89, 2000, reference 17 and Anasetti et al., Blood 84: 1320-1327,1994, reference 18). Lee et al. suggest that since the IL-2 receptor is expressed on activated lymphocytes, they hypothesized that daclizumab would be efficacious in deleting alloreactive T cells, and thus daclizumab should augment corticosteriod therapy. In this study, methylprednisolone (2 mg/kg) was given in conjunction with daclizumab (1 mg/kg). However, daclizumab did not augment the effect of methylprednisolone, and GVHD response rates at day 42 of the study were similar (see the abstract). The study was halted at when the combination therapy showed a significantly worse 100-day survival in the group receiving both methylprednisolone and

daclizumab. The overall 1-year survival rate was worse for the patient receiving the combination therapy, and there was increased mortality in those subjects that received the combination therapy. Lee et al. conclude that daclizumab and corticosteroids should not be used in combination for treatment of GVHD (see the abstract, last line).

This evidence demonstrates that even if an anti-interleukin 2 receptor antibody such as daclizumab and another agent are independently efficacious for the treatment of an immune mediated disorder, it clearly cannot be predicted that the combination would be effective (or act synergistically) for the treatment of that disease.

Also submitted herewith is Foster et al. ("Combo Therapies for MS: In trials, some pairings fare better than others," www.psychiatrictimes.com/display/article/10168/57451, July 26, 2008) (Exhibit E). This article describes the results presented at the Annual Meeting of the American Academy of Neurology (AAN), in Boston, April 28 to May 5, 2008. Foster reports that initial trials suggested that atorvastatin and glatiramer acetate were associated with clinical improvement in murine models of MS. However, when a clinical trial was conducted that combined atorvastatin with interferon-β1a (REBIF®) in humans, 10 of the 15 patients who received the combination therapy had new or enhancing MRI lesions, while only 1 of the 9 patients who received interferon-β1a alone had new or enhancing MRI lesions. Thus, two agents known to be of use for treating the same autoimmune disease will not necessarily be effective when administered in combination. More specifically, other agents known to be of use for the treatment of multiple sclerosis will not necessarily be efficacious when administered in combination with interferon-β.

Another study, termed the ACT study (Exhibit F), evaluated the effects of interferon-β in conjunction with methotrexate, pulsed intravenous methylprednisolone, or both. Although patients on the combination therapy appeared to have lower incidences of relapse and MRI lesions than the subjects on monotherapy, a statistically significant effect was not achieved (see page 2). Thus, the administration of other immunosuppressive agents, known to be effective for the treatment of MS, when administered in conjunction with interferon-1β, did not provide any therapeutic benefit.

Friese et al. discuss the results obtained by the present inventors with daclizumab (see page 1944). Specifically, Friese et al. disclose that based on the data relating to the role CD25+ cells in the EAE model (citing to Reddy et al., PNAS 101: 15434-15439, 2004, copy provided as Exhibit G) one

of skill in the art would have argued that there was no rationale for the use of daclizumab in the treatment of MS. Indeed, Reddy et al. disclose that anti-CD25 antibody treatment (which is another antibody that binds the IL-2 receptor) caused worsening of EAE in mice (see page 15435, first column). Thus, the effects obtained by the present inventors, as published in Bielekova et al. (PNAS 101: 8085-8, 2004), were surprising, and could not be predicted based on the prior art. Indeed Friese et al. state (page 1944):

> "IL-2 receptor blockade with the humanized anti-CD25 antibody (daclizumab) caused impressive reductions in MRI lesions and improvements in some clinical measures (Bielekova et al., 2004). In this case, the theoretical role of CD25 in promoting T regulatory cells, and equivocal EAE data (Engelhardt et al., 1989; Reddy et al., 2004), might have argued against its use in multiple sclerosis."

Thus, Friese et al. provide direct evidence that one of skill in the art would not predict that that the claimed methods would be effected based on any data obtained in the EAE model system, let alone the data of Hayosh and Swanborg on a completely different antibody.

Therefore, one of skill in the art would not view the claimed methods, directed to the combined use of daclizumab and interferon-beta as being obvious over (1) a description of methods that use another monoclonal antibody individually; (2) methods that use interferon-beta individually; (3) methods that utilize daclizumab individually; (4) teachings based on results obtained in the EAE model system or even (5) methods that use a monoclonal antibody for a completely different disease process.

IV. Even If The Claimed Combination Were *Prima Facie* Obvious, Unexpected Results Render the Combination Non-Obvious

The Guidelines state that Applicants can submit argument or evidence to demonstrate that the results of the claimed combination were unexpectedly superior. Submitted herewith is a copy of Rose et al. (Neurology 69: 785-789, 2007) (Exhibit H), which documents that the combination of daclizumab with interferon-1β can have an unexpectedly superior effect in some subjects with multiple sclerosis.

Rose et al. conducted a clinical trial wherein the daclizumab protocol developed by Martin and colleagues (the inventors of the present application). Specifically, daclizumab 1 mg/kg treatment was administered and administered two weeks later to subjects who had failed to respond to standard

interferon-1β treatment. The same dose was administered every 4 weeks for a total of 5.5 months along with continued interferon-1β therapy. Interferon-1β was discontinued if the patient had a cessation of Gadolinium contrast enhancing MRI lesions (CEL), and the same dose of daclizumab was continued for an additional 10 months. If CEL returned after cessation of interferon-1β, then interferon-1β therapy was restarted and daclizumab was administered at 1.5 mg/kg (see page 786). Nine patients continued in the study and completed the entire 27.5 month study period. Three patients had recurrent new CEL on daclizumab alone and were restarted on interferon-1β. Overall, daclizumab resulted in a decreased number of relapses (see page 787). Rose et al. concluded that daclizumab monotherapy could be effective in patients who have MS that is not controlled by interferon-1β. Rose et al. note that in 3 of the 9 subjects only the combination therapy was effective (see the discussion on page 788). Thus, in some patients who have failed therapy with interferon-1β alone, the combination of interferon-1β and daclizumab provides an unexpectedly superior effect as compared to monotherapy with daclizumab. This documentation of an unexpectedly superior effect overcomes any *prima facie* case of obviousness.

V. The Patient Population of Claims 20 and 21 Would Not Have Been Obvious

As stated in the Examination Guidelines the rationale to support a conclusion that a claim would have been obvious requires that all the clamed elements were known in the prior art. With regard to claims 20 and 21, none of the cited references teach the selection of a subject who has failed any other therapy, let alone treatment with interferon beta. Based on the cited prior art, it simply would not be predictable that a subject who failed one form of therapy would respond to another form of therapy. Specifically, none of the references provide any information that would lead one of skill in the art to modify the therapeutic regimens to select subjects who have failed therapy. In addition, there is nothing in the cited prior art that teaches that if a subject fails treatment with an agent, that the subject should be maintained on that agent, and administered additional agents. In other words, if a subject has failed therapy with interferon-1β, one of skill in the art would discontinue the administration of interferon-1β, and would not just continue the administration of interferon-1β in combination with other agents, such as daclizumab.

Paty et al. and Jacob et al. both teach the effectiveness of interferon-beta for the treatment of multiple sclerosis. They simply do not suggest treatments for subjects who fail interferon beta therapy.

Similarly, Hayoshi and Swanborg and Natkatani et al. teach the effectiveness of antibodies that bind the interleukin-2 receptor, but do not teach the selection of subjects that have failed any therapeutic regimen, let alone treatment with interferon-beta. Thus, the effectiveness of daclizumab in a subject who does not respond to interferon-beta is simply not a "predictable result" based on Paty et al, Jacob et al, Hayoshi and Swanborg and/or Natkatani et al. There is nothing that suggests that following a failure to respond to interferon-1β, a subject with multiple sclerosis should be continued on interferon-1β in addition to other agents.

Moreover, in the Supreme Court's opinion in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007), the Court explained that an invention is obvious if it is the result of ordinary skill and common sense. A corollary to this reasoning is that an invention is non-obvious if it runs counter to common sense. *See also In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984) (holding that a modification of a prior art device to be non-obvious when one of skill in the art would have expected the modification to render the device inoperable for its intended purpose).

The invention claimed in claims 20 and 21 is directed to a therapeutic regimen involving the administration of interferon beta to a patient who has previously failed to respond to interferon beta. If anything, one of skill in the art would have considered the therapeutic regimen of claims 20 and 21 to run counter to common sense because, for the claimed patient population of interferon beta non-responders, the interferon-beta treatment would be inoperable for its intended purpose. Accordingly, under the rationale of *KSR* and *In re Gordon*, the invention of claims 20 and 21 is nonobvious. The Examiner has not articulated any valid reason demonstrating otherwise.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claim 20 remains rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-21 and 29-34 of co-pending U.S. Application No. 10/607,598 ("the '598 application"), now issued as U.S. Patent No. 7,258,859 ("the '859 patent"). Several Office actions were received in the '598 application and are available in the U.S. PTO's electronic database (PAIR). The Applicants would be pleased to provide copies of these Office actions if for any reason the Examiner cannot access them on PAIR.

As to the merits of the rejection, an obviousness-type double patenting rejection is only appropriate where one or more claims of an application are either anticipated by or would have been obvious over the reference claims (here, the claims of the '859 patent). *See* MPEP § 804 (citing *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)).

The claims of the '859 patent are directed to methods for treating a subject with multiple sclerosis who has failed to respond to previous treatment with beta interferon with daclizumab in the absence of treatment with beta interferon.

The claims of the '859 patent do not anticipate the present claims: all the claims of the '859 patent specify a treatment regimen of daclizumab in the **absence** of treatment with beta interferon, whereas the present claims are directed to a treatment regimen of anti-interleukin 2 receptor antibodies (including daclizumab) **in combination with** interferon beta.

For at least the reasons explained in Section IV in the discussion of obviousness above, namely that combination therapy of multiple sclerosis with anti-interleukin 2 receptor antibody and interferon beta is unexpectedly superior over treatment of multiple sclerosis with anti-interleukin 2 receptor antibody alone, the presently claimed invention is nonobvious over the claims of the '859 patent.

Accordingly, the obviousness type double patenting rejection is in error and should be withdrawn.

CO-PENDING APPLICATION

Applicants would like to ensure that the Examiner is aware of co-pending application U.S. Patent Application No. 11/827,876 ("the '876 application"). No Office actions have been received in the '876 application.

CONCLUSION

Applicants believe that the present claims are in condition for allowance, which action is requested. The prior response included a specific request that if any issues remain prior to allowance, Examiner Hissong and/or Examiner Nichols contact the undersigned for an interview. However, the Examiners did not contact the undersigned, but issued a final Office action. The Examiners are again

formally requested to contact the undersigned, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request, and the prior request, were submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By _____
Susan Alpert Siegel, Ph.D.
Registration No. 43,121